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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,957	05/30/2006	Vladimir K. Khavinson	252185	7382

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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	
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04/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,957	KHAVINSON ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3-5* is/are allowed.

6)☒ Claim(s) *1 and 6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Claims 1, 3-9 are pending in the application.

Claims 1, 3-9 are presented for examination on the merits.

The tetrapeptide Lys-Glu-Asp-Trp-NH_2 [SEQ ID NO:1] was searched and found free of the prior art. The closest art found was that of Khavinson (US 7, 101,854), drawn to a tetrapeptide Lys-Glu-Asp-Ala, which does not read upon the instant claims. Claims 3-5 are deemed allowable. However, please see 112 1st and 2nd rejections below.

Specification

Sequence Compliance

Applicant is advised that the application is not in compliance with 37 CFR §§ 1.821-1.825.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR §§ 1.821- 1.825) in order to completely respond to this office action.

Specifically, the SEQ ID NO: was not included next to the tetrapeptides in page 3, lines 32 and 34; page 4, lines 1, 3, 6, 8, 10, 13-16, 21, 25-30; page 5, lines 12-14;

page 7, lines 4-5 (please note that this sequence is not the Sequence listing); page 7, lines 19-21; page 8, lines 12-13, 19-20, 22, 25-26, 29, 35; page 9, lines 1, 3, 6, 10, 11, 15, 19, 20, 24, 32, 34-35; page 10, line 1, 4, 7, 17, 22, 23-24, 29, 32; page 11, lines 4-6, 10-11, 14, 20, 22, 24, 30; page 12, 2, 4-5, 8-9, 19, 23, 26; page 13, lines 5, 18, 30, 33; pages 14-20, Tables 1-7. In order to satisfy the sequence rules requirements, Applicant needs to provide an amendment to the instant claims and specification to include reference to the appropriate "SEQ ID NO:".

In case of any new sequences not properly identified in the instant specification, Applicant is required to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, a new or substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. § 1.821(e) or 1.821(f) or 1.821(g) or 1.825(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. For rules interpretation Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.

Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Bio (<http://www.uspto.gov/ebc/efs/downloads/documents.htm>, EFS Submission User Manual - ePave)

2. US Postal Service:
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401 Dulany Street
Alexandria, VA 22314

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of diabetes, does not reasonably provide enablement for *preventing* diabetes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants have reasonably demonstrated/disclosed that the claimed compounds are useful as therapeutic agents for treating diabetes and/or reducing the risk thereof. However, the claims also encompass using the claimed compounds to treat pre-diabetic diseases and their complications, which is clearly beyond the scope of the instantly disclosed/claimed invention.

. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the invention. The claims are drawn to methods of treating or

preventing diabetes mellitus which consist in administering to the patient an effective amount of tetrapeptide Lys-Glu-Asp-Trp-NH_2 at least one day for a period necessary for attaining a therapeutic effect.

State of the prior art. At the time the invention was made, there was no vaccine available to treat pre-diabetic diseases and/or diabetes. The term diabetes mellitus includes type 1 diabetes (risk factors include autoimmune, genetic and environmental factors) and type 2 diabetes (is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity and race/ethnicity). [National Diabetes Fact Sheet, accessed online 4/7/08 at http://www.cdc.gov/diabetes/pubs/general.htm, page 1, paragraphs 1-3]. There are no known methods to prevent type 1 diabetes [National Diabetes Fact Sheet, page 2, paragraph 3]. Schatz et al. teach that type 1 diabetes is potentially preventable (page 3326, column 1) because knowledge that the immune system is involved in the disease and not only genetics, therefore providing for raised therapeutic possibilities because immunity can be manipulated (e.g., in vaccines). Schatz et al. also teach that the major diabetes prevention trials in the early to mid-1990s set out to determine whether progression to type 1 diabetes could be modified in high-risk individuals (e.g., islet autoantibody-positive relatives of an affected proband) with three different agents (nicotinamide, subcutaneous insulin, and oral insulin) and two huge study groups (the European Nicotinamide Diabetes Intervention Trial and the Diabetes Prevention Trial-Type 1) led to but one common result--- failure to prevent type 1 diabetes (page 3326, column 2).

Breadth of the claims. The claims are very broad, encompassing prophylaxis of any kind of diabetes mellitus in any patient.

Working examples. The specification provides examples of administration of Lys-Glu-Asp-Trp-NH_2. Example 2 (Table 1) is drawn to the administration in course of alloxan diabetes in 2 groups of about 10 white mongrel male rats; Example 3 (Table 2) is drawn to administrating intravenously to 15 mongrel male rats divided in 2 groups: the control group received saline solution and the other group received Lys-Glu- Asp-Trp-NH_2, followed by alloxan administration. 2 out of 8 rats treated with the tetrapeptide reported severe form of diabetes mellitus while in the control group there 5 out 7 developed severe diabetes mellitus. Example 4 (Table 3) is drawn to intraperitoneal administration. 23 white mongrel rats were divided in 3 groups: control (saline); second group 1 µg dosage and third group 10 µg. Example 5 (Table 4): 18 white mongrel male rats were divided in 2 groups, both groups were administered alloxan and then the control was given saline and the main group received 3 µg per rat. Example 6 (Table 5) was drawn to administration and measurement of glucose in 13 male rats used in other experiments, and 7 healthy rats, divided in 3 groups: Control, peptide administered and healthy. Example 7 (Table 6) is drawn to intravenous insulin in 3 groups of 6-8 rats each with glucose concentration measurement afterwards. Example 8 (Tables 7-8) is drawn to 23 patients with type 1 diabetes, 13 patients with type2 diabetes consisting of administration of the tetrapeptide and saline alongside with insulin treatment which was adjusted as needed.

Guidance in the specification. The specification provides little guidance regarding practice of the claimed prophylactic methods with respect to, e.g., diabetes type 1, diabetes type 2, gestational diabetes and other types (e.g., National Diabetes Fact Sheet, page 1).

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). In the instant application, Applicants claim methods of treating and preventing diabetes mellitus in general, including type 1 and type 2 diabetes. Please note that the terms "prevention" and "prophylaxis" are absolute terms, which mean to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes) - including preventing such disorders as pre-diabetic disorders and their complications (which clearly are not recognized in the medical art as being totally preventable conditions).

Amount of experimentation necessary. Besides the general expectation that it will require years of further research to develop a therapy for prevention of diabetes (see Schatz et al. e.g., page 3326) and that type 1 diabetes is currently not preventable, (see above) it would require extensive research to understand the fundamental biology of the system, including the genetic, environmental and immune components of diabetes type 1 and pre-diabetic states for diabetes in general. Applicants have identified a method to treat diabetes, however, in regards to the prophylactic and pre-diabetic disease treatment aspects in any subject, one example (Example 3) was presented which does

use a small sample of rats which received the tetrapeptide before being exposed to a chemically induced diabetes, but this example does not account for the many factors (such as immune, genetic, environmental) which affect the onset of different types of diabetes, and therefore essentially all of the complex work and clinical experimentation required to ultimately develop a prophylactic treatment has been left for others. Schatz et al. indicate that a complex combination of multiple factors needs to be included in further prevention trials, such as including nutritional interventions, antigen-based therapies, monoclonal antibodies and other immunoregulatory and immunosuppressive agents. Schatz et al. conclude that "[r]umors of death of diabetes prevention may have been exaggerated, but there are no easy victories in sight" (page 3327, last paragraph). For the reasons discussed above, it would require *undue experimentation* for one skilled in the art to use the claimed methods.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is rendered vague and indefinite by the phrase "Tetrapeptide lysyl-glutamyl-aspartyl-tryptophane amide of the general formula Lys-Glu-Asp-Trp-NH_2 [SEQ ID NO: 1]" because it is not clear whether the claim is to a single tetrapeptide of formula lysyl-glutamyl-aspartyl-tryptophane amide or if it is meant to include tetrapeptide derivatives of this compound which still have the general formula

Lys-Glu-Asp-Trp-NH_2 such as side chain derivatives thereof, alkylated terminal amides and so forth. If the tetrapeptide Lys-Glu-Asp-Trp-NH_2 [SEQ ID NO: 1] is the only one intended to be claimed, the transitional phrase "consisting of" is suggested, i.e., tetrapeptide consisting of SEQ ID NO: 1.

Conclusion

Claims 3-5 are allowed. Claims 1, 6-9 are rejected. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

MMCG 04/08